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# BULLETIN

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*Original Articles*

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# CHEMOTHERAPY IN MALARIA*

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Most of the recent advances in the chemotherapy of the malarias can be presented in the form of a commentary on the program of studies carried out under the auspices of the Office of Scientific Research and Development during the past four years. The studies were initiated in 1941 through the agency of the Committee on Medical Research with the aid of committees set up in the Division of Medical Sciences of the National Research Council.[1,2] The committees concerned with malaria underwent changes with the progressive expansion of the scope of the studies until, in the winter of 1943-44, the present program was evolved under the sponsorship of the Board for the Coordination of Malarial Studies and its various Panels. The Board is a coöperative endeavor and involves the participation of the Committee on Medical Research, National Research Council, Army, Navy, United States Public Health Service, and a group of investigators in civilian institutions under con-

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The information contained in this paper is largely derived from work now sponsored by the Board for the Coordination of Malarial Studies and carried out by investigators of various institutions through contracts between them and the Office of Scientific Research and Development which were recommended by the Committee on Medical Research.

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tract with the Office of Scientific Research and Development.

The primary purpose of the investigations has been, at all times, to satisfy specific needs of the armed services. Information was required which would permit the better management of the malarial hazard first, as a factor of operational significance to combat troops in hyperendemic areas, and second, as a problem relating to the maintenance of good health of troops while they were in and after they had been removed from such an area. It was apparent from a consideration of these needs that initially, considerable work must be performed with antimalarial agents already available so that they could be used to the best advantage. However, it also seemed likely, that advantages would accrue were new and more effective antimalarials developed. More specifically, it was hoped that among the newer agents there would be one or more which would either prevent malarial infections or effect definitive cures at well tolerated dosage.

The direction of the early clinical work (1942-1943) was conditioned largely by the early loss to the United Nations of their normal sources of supply of quinine and by the lack of an adequate stockpile. Those who were intimately concerned with the malarial problem during the first year of the war will recall the gravity of the situation. The worry which was incidental to the lack of an adequate supply of quinine was enhanced by the preliminary reports from the field which carried the suggestion that quinacrine was of little use in the suppression and treatment of the malarias and that pamaquin as then used had little value in the cure of vivax malaria.

*The Investigation of Quinacrine:* Quinacrine was said to be unable to produce a prompt termination of the clinical attack, more particularly, in falciparum malaria, much less a cure in either falciparum or vivax malaria. In addition, it was reported to be both highly toxic and relatively ineffective when used as a suppressive. These experiences caused many medical and line officers to believe that the control of malaria by quinacrine was not practicable. The clinical results were at such variance with reports in the literature[3] that an uncertainty existed in the minds of some as to the chemical identity of German and American quinacrine. This uncertainty was sufficiently serious to require the services of a number of chemists, pharmacologists and clinicians, the integrated efforts of which established the identity of the two products by the summer of 1942.[4] Even so there was a growing belief

that quinine was the only known antimalarial agent of consequence, that such of it as was available must be used sparingly,[5] and that a substitute for quinine, with all its limitations, was not only highly desirable, but urgently needed.

The initial confusion concerning the therapeutic efficacy of quinacrine resulted from the lack of information which would permit its use in a rational manner. Empirical dosage schedules had been established at an earlier date and were generally used by the services.[6] These were based upon studies performed in the 1930's on groups of individuals with varying degrees of acquired immunity.[3] The dosage schedules which were found to be effective in such individuals are now known to be generally ineffective when applied to those who are wholly susceptible to these diseases. Furthermore, the recommended dosage regimen of suppressive quinacrine therapy brought into sharp focus the gastrointestinal irritation which frequently accompanies the oral administration of doses larger than 0.1 gram for suppressive purposes.

It is now established that quinacrine is a generally useful and highly effective antimalarial, quite superior to quinine in most situations.[7] This important advance in our knowledge resulted from the development of chemical methods for the estimation of quinacrine in biological fluids and tissues[8, 9] and the use of these methods in studies which defined the antimalarial activity and physiological disposition of the drug.

It was first demonstrated in the winter and spring of 1943 that the inherent antimalarial activity of quinacrine is high and is related to its concurrent plasma concentration,[10] and that quinacrine is very extensively localized in the tissues of the body and degraded and excreted at low rates. It seemed reasonable to believe that the efficacy of suppressive quinacrine therapy would depend more upon the total dosage administered per week than upon the specific pattern of the dosage regimen. It also seemed reasonable to believe that, since a quick therapeutic effect only obtains when a high plasma quinacrine concentration is reached early in the course of therapy, the efficacy of quinacrine in causing an abrupt termination of a clinical attack would depend largely upon the amount of drug administered during the first 24 hours of therapy.[11, 12]

These concepts were quickly translated into practical regimens of therapy which have been in use by the Army and Navy for some two years.[13] As the result of this experience, it is known that effective sup-

pression of malaria in the adult requires the administration of 0.1 gram of quinacrine daily; also to derive the maximal benefit, the drug should be administered for some two weeks prior to entry into an hyperendemic area and for some weeks after the risk of infection no longer exists. Prompt control of the clinical attack in vivax and falciparum malaria and cure in the latter infection can be accomplished by the administrtaion of 0.8 to 1.0 gram of quinacrine in divided doses during the first 12 to 18 hours of treatment and 0.1 gram three times daily for an additional six days, or, an equivalent amount in a shorter period of time.

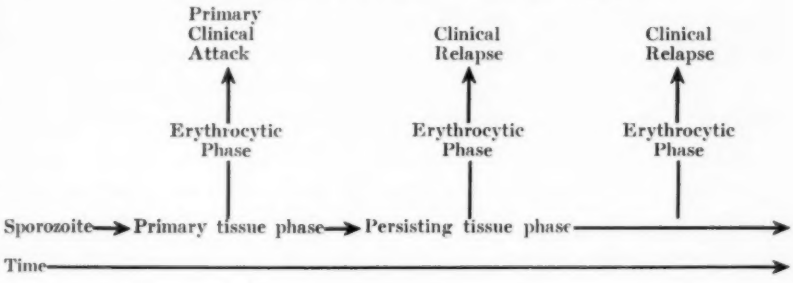
The establishment of quinacrine as a highly effective routine antimalarial permitted the clinical facilities of the civilian program to be directed towards the attainment of other objectives. This was because the proper usage of quinacrine had largely removed malaria from the field of tactical importance to the Services.

A consideration of the subsequent studies, which were aimed very specifically at the development of a curative agent in vivax malaria, requires a definite understanding of the specific limitations of quinacrine. It will prevent the inception of clinical falciparum malaria when given as a suppressive, and effect a prompt and definitive cure when the infection is once established. However, quinacrine will not prevent the inception of vivax malaria although it is highly effective in suppressing its clinical manifestations, and, it will not effect a definitive cure when the infection is once established. These two limitations are fundamental in nature. The drug has other limitations but these are of lesser importance. It is prone to cause gastrointestinal reactions when administered for suppressive purposes in single doses in excess of 0.1 gram. This is of some consequence since it increases the administrative burden of suppressive therapy, requiring as it does a daily dose of drug. The yellow staining of the skin which is a constant finding with quinacrine therapy may also be mentioned since it is an undesirable feature. Other toxic manifestations are too infrequent to warrant special attention at this time.

*The Search for new more Effective Antimalarials (Suppressives):* An understanding of the biological basis for the most important fundamental limitation of quinacrine, i.e., its inability to cure vivax malaria, and the design of experiments to discover antimalarials not having a similar limitation require an appreciation of some of the important features of the biology of the malaria infections. The disease mechanisms

FIGURE I

PROPOSED SCHEME TO DESCRIBE THE UNDERLYING DISEASE MECHANISM OF VIVAX MALARIA




which underly the human infections may be assumed to parallel, in certain respects, those which have been described in some detail for several avian infections.[14] A general outline of a mechanism which seems reasonable for vivax malaria[12] is presented in the accompanying figure (Figure 1). Consideration is not given to the sexual forms of the parasite, i.e., the gametocytes. These have no importance in conditioning the clinical course of the disease in the individual patient.

Such an outline assumes that, subsequent to the deposition of sporozoites by the mosquito, a tissue phase of the developing plasmodium is established and persists for a considerable period of time. It is further assumed that lines of erythrocytic forms of the parasite are derived from the tissue phase as discrete episodes in the course of the disease. These in turn are responsible for the initial attack and the parasitological and clinical relapses which are characteristic of vivax malaria. The early portion of the disease mechanism in falciparum malaria appears to be similar to that of vivax malaria in all respects. However, there is no need to assume the life history of the falciparum parasite also includes a persisting tissue form since this type of malaria does not systematically relapse. If a persisting tissue form is present in falciparum malaria, then it poses no special therapeutic problem since, contrary to vivax malaria, the disease can be cured by a variety of chemotherapeutic agents which are also highly effective against the erythrocytic forms of the plasmodium.

It will be appreciated from such a summary, that the malarial parasite has a rather complex life history within the human host when the infection is acquired naturally. This involves several phases of develop-

ment each of which may be expected to differ from the others as to morphology, metabolic characteristics, and the cell type of the host within which it takes place. It will also be appreciated that potentially there are several types of antimalarial activity in the vivax infection. For convenience these may be designated as prophylactic if the action is on the sporozoite or the primary tissue forms of the plasmodium, as suppressive if on the erythrocytic forms or as curative if on the persisting tissue forms.

Each of these types of antimalarial activity may be examined separately. The testing for prophylactic or curative activity requires the use of mosquito induced malaria. The latter is further complicated by the need for a long term observation period before a final judgment can be made on the extent to which a given drug or a given dosage regimen is curative. However, suppressive antimalarial activity is amenable to simple and rather precise assay by the use of blood induced infections.[15] This type of infection has a more simple disease mechanism. It is established by the simple transfer of infected blood from a patient with an active infection and having only the erythrocytic phase of the disease; it permits the examination of the suppressive type of activity alone. It is important to note that the differences in suppressive and curative activities could be either quantitative or qualitative. Consequently, the development of an antimalarials with a high degree of curative action in vivax malaria could be approached with reason by more than one way.

One approach could be based upon an hypothesis which held the fundamental metabolic organization of the persisting tissue forms of *P. vivax* to be essentially the same as that of the erythrocytic forms of the plasmodium. Due to differences in their environments, the tissue form was assumed to be less susceptible to the antimalarial effect of drugs such as quinacrine. Accordingly, a reasonable approach to the development of curative agents appeared to lie in the direction of obtaining more active drugs as evidenced by their ability to exert an action upon the erythrocytic forms of the parasite, i.e., as manifested in the blood-induced infection. It was hoped that if the intensity of this type of antimalarial activity was sufficiently great in the case of any drug then it would not only interrupt the erythrocytic phase of the vivax parasites but would also obliterate the persisting tissue phase of a naturally acquired infection and so cure the disease.

Another approach could be based upon an hypothesis which held

the fundamental metabolic organization of the persisting tissue forms of *P. vivax* to be different from that of the erythrocytic forms of the plasmodium, at least insofar as the susceptibilities of their essential biological systems were concerned. Accordingly a chemotherapeutic agent might affect the tissue forms through an action which was qualitatively different from any which produced a dramatic effect upon the asexual forms in the erythrocyte, i.e., the blood-induced infection had little value in the search for curative agents. In accordance with this hypothesis, it would be quite possible to miss a curative agent unless a number of representatives of each group of chemicals studied were examined for curative action. Compounds could then be selected for this type of activity because of special activities other than suppressive in the avian infections, or, they could be screened for curative action in the human vivax infection without prior experimental trial.

It was generally agreed in the fall and winter of 1943 that, sufficient evidence was not available for one to decide which of these two hypotheses was more reasonable. Consequently, there was considerable discussion, as to whether blood-induced infections could be of value in a program, the end of which was the development of curative agents for vivax malaria. However, this type of infection was continued in use on a rather extensive scale, its use being based on the tentative acceptance of the reasonableness of the first working hypothesis. As a logical consequence and as the major effort at that time, a systematic attempt was made to increase antimalarial activity in a number of the chemical series then under exploration and the best representative in each series was selected on the basis of information from blood-induced infections, and examined for curative action in mosquito induced vivax malaria. Actually the overall procedure adopted represented a partial compromise between the two working hypotheses. Certain of the compounds studied for curative action had relatively little suppressive action, their selection being based upon two considerations. They were representatives of chemical series as yet untried for curative action and although they might have had little suppressive activity, the compound tested was better in this respect than the other members of the series examined. In addition any compound showing a special type of activity in the avian infections, such as curative or prophylactic, was also tried for curative action in vivax malaria.

The advantages of this approach, at that stage of the program, were

three. First, it was believed likely, with the leads then available, that suppressive antimalarial activity could be increased many fold in several different types of compounds and, as the result of this effort, compounds would shortly become available with which to test the correctness of the first working hypothesis. Second, it would permit the study of a number of chemical series, as yet unexamined, for their possession of curative action and perhaps establish a correlation between special activities in avian infections and curative activity in vivax malaria. Third, it seemed reasonable to suppose that this approach to the problem would result in the development of antimalarials superior to quinacrine although they might have the same fundamental limitations. The third possibility was important. It was desirable to have available antimalarials other than quinacrine should the long-term continuous administration of quinacrine to the human be accompanied by toxic manifestations which at the time could not be predicted.

It was early demonstrated beyond doubt that the suppressive antimalarial activity of a compound, when measured in a single avian infection, may have little prediction value for the situation obtaining in the suppression of peripheral parasitemia in the human malarias.* It was later demonstrated that the sum total of the information, when derived from the study of the activity of a compound or series of compounds in several avian infections using several avian hosts, does have fair prediction value in the selection of compounds for trial as suppressives in the human malarias. Lastly it was demonstrated, with 1 the compounds studied, that none had higher antimalarial activity of a suppressive nature in both human infections that had been observed in at least one of the avian infections.** This information was accumulated incidental to the survey of a very large number of compounds (ca. 14,000) for activity in the avian infections, the survey of a limited number of compounds (ca. 65) for suppressive activity in the human infections and a selected number of the latter group (ca. 20) for prophylactic and curative action in vivax malaria.

Out of these extensive studies no compounds were developed with prospects of being useful as curative agents in vivax malaria although

* The data available on antimalarials at the beginning of the program and those from allied fields of chemotherapy led Doctor E. K. Marshall, Jr., Chairman of the Pharmacological Panel, to this conclusion.

** The substantiation of these general concepts was as the result of the combined efforts of all Office of Scientific Research and Development contractors on both the pharmacological and clinical levels. The experimental facts themselves will be contained in a monograph entitled "A survey of antimalarials 1941-1946," edited by Doctor F. Wiselogle and prepared by The Office for the Survey of Antimalarial Drugs. This monograph should be available by the summer or fall of 1946.

several have unquestioned advantages over quinacrine and quinine. For example, a plasma quinine concentration of 5 mg. per liter maintained for four days terminates a blood induced infection or a clinical attack of a mosquito induced infection due to the McCoy strain of *P. vivax*.[10] An equivalent effect will be produced by 30 micrograms per liter of quinacrine.[10] However, plasma concentrations of quinine in excess of 12 mg. per liter and of quinacrine in excess of 150 micrograms per liter are not generally well tolerated.

Of the newer compounds developed during the fall and winter of 1944-1945, there is one (SN-7618)* which is rather well tolerated at dosage schedules which produce plasma drug concentrations some 30 times those required to terminate the clinical attack.[16] Others, where activities have been placed less precisely in terms of plasma drug concentrations, can be administered in daily doses many many times those required to produce a demonstrable antimalarial effect. Nevertheless, these agents have nothing to offer as curative agents in vivax malaria. It may be concluded from these observations that the major working hypothesis selected for trial in 1943 in the attempt to develop curative agents in vivax malaria is not correct.

Before considering the next phase of studies it will be of some interest to take note of the potentialities of certain of the agents which, at least to some extent, are by-products of an unsuccessful attempt to produce a curative agent for vivax malaria. Among the more promising compounds are some which may be expected to effect complete suppression when administered once weekly in a well tolerated dose. They will also effect an abrupt termination of a clinical attack of vivax and a cure of falciparum malaria when administration is limited to one or at most, two days. None of these highly effective agents has, as yet, been fully exploited. However, information is at hand which permits the prediction that they will constitute a relatively simple means for the complete control of malaria in many areas due to the lessening of the administration problem of suppressive therapy as compared to quinacrine. They may also, in specific areas, contribute to the eradication of the malarias through their ability to curtail transmission of the disease. Exploration of the advantages to be derived from the use of some of these newer agents is now under way.

* SN-7618 is *7-chloro-4-(4-diethylamino-1-methylbutylamino)* quinoline. Several closely related compounds have comparable activity.

*The Search for More Effective Antimalarials (Curative):* Of importance to the attainment of one of the ultimate objectives of the program, was the conclusion that a simple increase in antimalarial activity as evidenced by an effect against the erythrocytic forms of the parasite cannot, *per se*, be expected to lead to curative drugs for vivax malaria. The obtaining of this information marked the beginning of the present stage of the malaria studies. This has been characterized by the direct approach to the problem of devising curative agents which are now assumed to require qualitatively different actions than those which are simply reflected in a reduction of peripheral parasitemia in vivax and falciparum malaria. These studies are proceeding in several laboratories and with some prospect of success.

A serious obstacle to success in this endeavor stems from the fact that, with our present knowledge, it is not possible to use the experimental avian malarias effectively to screen compounds prior to their selection for trial as curative agents in vivax malaria. Drugs have been developed which possess prophylactic and/or curative action in one or another of the avian infections but, generally speaking, these actions are not a reflection of a similar action in vivax malaria. Actually, there is, as yet, no general correlation between these special actions in the avian infections and comparable action in the human infections. The promise that curative drugs will eventually be found stems solely from the recent confirmation of the earlier studies on the curative action of pamaquin, an 8-aminoquinoline.

It seems reasonably certain that the older investigations on the antimalarial activity of pamaquin led to conclusions which are essentially correct.[17] That is, pamaquin, when administered at high dosage, has a curative action in vivax malaria when administered concurrently with quinine over a long period of time. This is a fact of importance. It demonstrates that the persisting tissue forms of the plasmodia which are held to be responsible for the relapse in vivax malaria are subject to the lethal action of a drug to which the type of host cell within which they reside is not also generally susceptible. Furthermore, the curative action of pamaquin makes available a specific lead towards the synthesis of better tolerated curative agents.

This synthetic lead is now being explored extensively. It did not receive attention earlier in the program for three reasons. It was known that pamaquin analogs had received systematic study by the Germans,

French, and Russians, both before and after the development of pamaquin, and no better drug had been announced. It was also known that pamaquin and many of its analogs possess seriously toxic effects when administered at a dosage well below that which is generally curative. Finally, it was hoped that a curative agent might be found in other series of substances which were characterized by lesser toxicity. It was not until the last possibility seemed unlikely, at least in the near future, that it was deemed advisable to embark upon an extensive study of 8-aminoquinolines.

It is now known that previous exploration of the 8-aminoquinolines was inadequate to be certain that pamaquin is the best drug to be derived from this series. Furthermore, the careful study of the antimalarial activity and toxicity of pamaquin and a selected series of 8-aminoquinolines seems to indicate that such an exploration will be profitable. A consideration of what has been done with other chemical series, whereby one or another aspect of antimalarial activity has been greatly increased without a comparable increase in toxicity, makes the prospect of obtaining a useful agent from this group of substances rather bright though highly speculative.

Should it happen that generally useful curative agents for vivax malaria are contained in the series of 8-aminoquinolines, this will make an interesting chapter in the development of antimalarial agents. Pamaquin was first used on a very extensive scale in the late 1920's. It was said, on the basis of preliminary studies, to possess some suppressive effect upon the erythrocytic phase of vivax malaria, as well as a curative action in this disease. It was also said to have little or no suppressive effect upon the erythrocytic phase of falciparum malaria but a dramatic effect upon the gametocytes of the plasmodium responsible for this infection. In addition it was said to be a true prophylactic in each infection.

Shortly after the drug was available for large scale experimental use it became apparent that the dosage recommended in the earlier studies could be expected to produce widespread and seriously toxic effects. However, the extent of the toxicity was not appreciated at a sufficiently early date to prevent the organization of reasonably well controlled trials to assay the curative action of pamaquin in vivax malaria.

It was common practice at that time to treat both vivax and falciparum malaria with full therapeutic doses of quinine, about 2.0 grams

daily, for some 14 to 21 days. Consequently, when pamaquin was tested it was also administered for this period of time. It was demonstrated quite early that a combination of concurrently administered pamaquin and quinine is superior to the administration of either drug alone. For example, in one series[17] there was observed 75 per cent relapses in an eight weeks period with quinine alone, 25 per cent with pamaquin alone and essentially none with a combination of the two antimalarials. The dosage of pamaquin in these studies, calculated as the hydrochloride was as low as 40 mg. daily in many patients. It is possible that such a dosage regimen would have come into general use despite the toxic effects of the pamaquin except for the discovery and limited exploration of quinacrine which occurred about this time.

It was found, with quinacrine, that little advantage is derived from the administration of quinacrine beyond a seven day period of treatment at 0.1 gram three times a day in population groups having a fair degree of immunity. As a reaction to this finding, the belief gained credence that quinine administration might also be curtailed to a similar period with advantage. This belief together with a growing appreciation of the toxic hazard of pamaquin led to a curtailment in the duration of the administration of quinine as well as a lowering of the pamaquin dosage commonly used. It is not surprising then, that the publications of the League of Nations recommended that combination pamaquin and quinine therapy be limited to seven days with the daily dose of pamaquin no higher than 30 mg. of the hydrochloride. The increase in the toxicity of pamaquin when administered concurrently with quinacrine led to the adoption of a convention whereby pamaquin was administered in similar dosage but for only five days and separated from quinacrine administration by a three day drug free interval. It is now known that pamaquin administered at such a dosage and in such manner has little to offer as a curative agent in vivax malaria although it is a highly effective gametocidal agent. It seems likely that the early studies with pamaquin produced a different therapeutic result because the dosage was usually higher, administration was for a longer period of time and the drug was administered concurrently with quinine. However, all three features were lost sight of in the years between 1931 and 1941 so that, the early recommendations for the use of pamaquin by the services were not of the type that would be expected to yield a significant proportion of cures.[6]

Work during the past year has retraced these steps and it is believed that the examination of the curative action of the 8-aminoquinolines is again on a sound experimental basis. However, progress towards the ultimate goal of these studies will be slow since, at the moment, it is necessary to restrict the primary examination of compounds in this series for curative action to human experimental material.

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# SOME EFFECTS OF THE RICE DIET TREATMENT OF KIDNEY DISEASE AND HYPERTENSION*

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KIDNEY cells can be kept "alive" for a few hours in the Warburg apparatus and their chemical reactions examined in a rather simplified set-up.[1] Tissue slices thin enough to permit optimal diffusion are suspended in salt solutions, serum or exudate. The concentration of oxygen, carbon dioxide, sodium bicarbonate, sugar, aminoacids, ketoacids, lactic acid, etc., in the suspension milieu can be quantitatively controlled. Factors such as the rate of arterial and venous blood flow, the lymph flow, and the excretion of urine do not complicate the experiment. From one five-minute period to another one can measure manometrically what these isolated kidney cells do under varying conditions.

Like all other animal tissue, kidney cells have two main sources of energy, oxidation and fermentation. Values of about 10 are given in the literature for $BO_2$ and $QM_{N_2}$ of human kidney cortex,[2,3] i.e., the approximate amount of oxygen used for oxidative processes by 100 Gm. of fresh kidney substance would be about 5 liters in 24 hours; the approximate amount of lactic acid formed anaerobically in the same time would be about 2 Gm.

If in the course of a disease, renal tissue is destroyed and replaced by a scar, obviously the only metabolic reactions to be found will be those of the scar tissue and no longer those of the kidney cells. Between normal and completely destroyed cells, there are as far as disturbances of cellular metabolism are concerned, the following possibilities:

1. The cells are uninjured, but metabolize in a pathological environment.
2. The cells are injured, but the environment in which they metabolize is normal.

* From the Department of Medicine, Duke University School of Medicine, Durham, N. C. Read January 15, 1946 before the Section of Medicine of The New York Academy of Medicine.

TABLE I—CHANGES IN CHEMICAL COMPOSITION OF "INFLAMMATION FLUID"

| | *Serum* | *Fluid from Sterile Blister of Skin (Normal person)* |
|---|---|---|
| Oxygen (mm. Hg.) | 110 | 6 |
| Sugar (mg./100 cc.) | 90 | 6 |
| Lactic Acid (mg./100 cc.) | 10 | 125 |
| Bicarbonate ($10^{-3}$ molar) | 25 | 9 |
| PH | 7.4 | 6.3 |

3. The cells are injured and metabolize in a pathological environment.

In order to learn something about the chemical composition of such a "pathological environment" we measured the metabolic reactions which take place during an inflammation. We produced sterile cantharidin blisters on the skin of normal people and of patients with various diseases and measured the metabolism of the leukocytes in the blister fluid and the chemical changes produced by them.[4] As Table I shows, the concentration of some biologically essential substances shows a decisive change during inflammation.

The next step was to determine what effects on the metabolism of kidney cells were produced by these environmental changes. We found the anaerobic splitting of sugar into lactic acid to be markedly dependent on changes of the sodium bicarbonate, sugar, and hydrogen ion concentration. The rate of oxidation was, to a large extent, independent of sodium bicarbonate, sugar, and PH, but was dependent on variations of oxygen concentration.

We could show further that the deamination of aminoacids and the formation of ammonia by slices of kidney tissue are inhibited by lowered oxygen concentrations. This applies both to the so-called "unnatural" d-aminoacids and to those naturally present in the plasma of man, rat, and rabbit, and in the tissue slices themselves.[5]

Besides the inhibition of the rate of deamination, which is reversible, there is another effect of low oxygen concentration on kidney cell metabolism which causes irreversible changes. If we kept slices of

kidney tissue for about one hour in an oxygen free atmosphere and then re-established conditions of optimal oxygen concentration the cells were still able to deaminize aminoacids and to form ammonia but they had lost the ability to oxidize ketoacids.[6] This means that by the removal of oxygen for a given time one can injure kidney cells selectively as to their oxidative reactions.

The obvious question is: What practical significance have these cellular physiological findings in the treatment of diseases in which renal metabolic dysfunction may play a role. Some simple examples may show the trend of our reasoning. Let us assume that the oxygen *supply* to any one kidney cell has been decreased by some pathological condition and that we are unable to increase it; still, it might be possible to increase the oxygen *concentration* by reducing the amount of work required from this cell, thus decreasing its oxygen demand. Or let us assume that the rate of oxidation of ketoacids in any one diseased kidney cell is decreased; still, it might be possible to reduce the amount of ketoacid offered to the cell if we were able to remove from the diet those substances from which ketoacids are derived. Deductions of a similar kind might be drawn from observation of the role played in renal metabolism by aminoacids, sugar, sodium bicarbonate, etc.

It would be most desirable, of course, to substitute for the natural ferments that have been destroyed, extracts of animal kidneys, or even better, synthetic substances with the same chemical properties as those in normal kidney cells. Unfortunately, such substances are not yet available.

I have been asked to speak to you this evening about a less perfect approach, but one which has led to rather satisfactory results: the compensation of renal metabolic dysfunction with the rice diet.

The consensus of opinion at the present time is that dietary treatment is useful in kidney disease, but of little or no value in hypertension without obvious renal involvement. Goldring and Chasis in 1944 summed up the prevalent view in their book on hypertension: "The diet in uncomplicated hypertension requires no essential change from the normal."[7]

Compared to diets previously used in hypertension, the rice-fruit-sugar diet is rigid. It contains in 2000 calories about 5 Gms. of fat and 20 Gms. of protein derived from rice and fruit, and not more than 0.2 Gm. of chloride and 0.15 Gm. of sodium.[8]

TABLE II—SERUM CHOLESTEROL OF PATIENTS WITH HYPERTENSIVE VASCULAR DISEASE ON RICE DIET

(Mg. per 100 cc. of serum)

| *Case* | *Before* | *After* | *Days* |
|---|---|---|---|
| 1. | 205 | 178 | 67 |
| 2. | 220 | 191 | 42 |
| 3. | 168 | 175 | 240 |
| 4. | 173 | 170 | 56 |
| 5. | 225 | 177 | 143 |
| 6. | 238 | 200 | 61 |
| 7. | 248 | 200 | 156 |
| 8. | 255 | 215 | 47 |
| 9. | 290 | 150 | 288 |
| 10. | 354 | 275 | 134 |
| 11. | 242 | 172 | 72 |
| 12. | 292 | 237 | 212 |
| 13. | 234 | 173 | 73 |
| 14. | 187 | 186 | 85 |
| 15. | 325 | 226 | 31 |
| 16. | 260 | 192 | 110 |
| 17. | 217 | 190 | 125 |
| 18. | 212 | 176 | 130 |
| 19. | 228 | 166 | 35 |
| 20. | 317 | 186 | 52 |
| 21. | 224 | 155 | 32 |
| 22. | 172 | 160 | 35 |
| 23. | 218 | 135 | 90 |
| 24. | 221 | 192 | 40 |
| 25. | 255 | 146 | 139 |
| 26. | 210 | 225 | 228 |
| 27. | 230 | 164 | 35 |
| 28. | 300 | 198 | 6 |
| 29. | 231 | 213 | 166 |
| 30. | 209 | 181 | 12 |
| 31. | 250 | 247 | 32 |
| 32. | 250 | 260 | 65 |
| 33. | 252 | 161 | 14 |
| 34. | 185 | 108 | 14 |
| 35. | 188 | 150 | 83 |
| 36. | 300 | 203 | 45 |
| 37. | 284 | 235 | 18 |
| 38. | 230 | 228 | 21 |
| 39. | 332 | 246 | 14 |
| 40. | 137 | 175 | 28 |
| 41. | 283 | 205 | 203 |
| 42. | 238 | 210 | 84 |
| 43. | 333 | 270 | 28 |
| 44. | 266 | 154 | 112 |
| 45. | 345 | 258 | 74 |
| 46. | 293 | 200 | 20 |
| 47. | 268 | 170 | 133 |
| 48. | 302 | 217 | 100 |
| 49. | 222 | 70 | 99 |
| 50. | 210 | 190 | 109 |
| 51. | 300 | 225 | 166 |
| 52. | 242 | 152 | 126 |
| 53. | 145 | 188 | 21 |
| 54. | 220 | 166 | 105 |
| 55. | 290 | 160 | 102 |
| 56. | 195 | 168 | 21 |
| 57. | 318 | 235 | 9 |
| 58. | 220 | 187 | 53 |
| 59. | 246 | 220 | 136 |
| 60. | 210 | 205 | 24 |
| 61. | 225 | 200 | 16 |
| 62. | 273 | 230 | 9 |
| 63. | 210 | 143 | 43 |
| 64. | 215 | 155 | 221 |
| 65. | 230 | 153 | 17 |
| 66. | 210 | 175 | 212 |
| 67. | 292 | 168 | 78 |
| 68. | 215 | 110 | 76 |
| 69. | 239 | 149 | 60 |
| 70. | 192 | 215 | 24 |
| 71. | 308 | 246 | 155 |
| 72. | 258 | 175 | 41 |
| 73. | 193 | 153 | 16 |
| 74. | 260 | 170 | 178 |
| 75. | 168 | 160 | 240 |
| 76. | 317 | 170 | 146 |
| 77. | 200 | 175 | 6 |
| 78. | 304 | 169 | 66 |
| 79. | 186 | 102 | 205 |
| Average: | 243.2 | 185.9 | |

Average Difference 57.3 mg.

It has been argued that this diet is nothing but starvation and that at least the "wear and tear quota" of 45 Gms. of protein is needed to maintain protein equilibrium. This figure, however, has no other basis than the 7 Gms. of nitrogen excreted per day by people who are fasting and represents only the body's effort to meet its caloric requirements by breaking down its own protein. The daily urinary nitrogen excretion of patients who have followed the rice diet for two months or more averages 2.26 Gms., which means that with a daily intake of little more than 15 Gms. of protein due to the protein sparing effect of carbohydrates, the nitrogen equilibrium is maintained.[9] In fasting, the daily urea nitrogen excretion in the urine is about 5.5 Gms. The average daily urea nitrogen excretion in the urine of patients who have followed the rice diet for two months or more is 1.1 Gms.[9]

In fasting, the blood urea nitrogen concentration is higher than it is normally. In patients on the rice diet, the urea nitrogen concentration is below the level of normal (average of 6.6 mg. per 100 cc. of blood). In starvation, hemoglobin and plasma protein concentrations decrease; in patients on the rice diet, the hemoglobin and plasma protein levels are maintained.[9]

It has been argued that the restriction of fat in the rice diet is too rigid and that patients with hypertension should eat "well-balanced meals." On the other hand the relation between hypercholesterolemia and hypertensive vascular disease has been stressed repeatedly, especially with regard to vascular retinopathy, coronary disease, and arteriosclerosis. In a series of 79 patients with hypertensive vascular disease 53 (i.e., 67 per cent) had a cholesterol concentration of at least 220 mg. per 100 cc. serum at the beginning of the treatment. As Table II shows, the hypercholesterolemia decreased with the rice diet in 52 of the 53 patients, the average decrease being 74 mg. per 100 cc. serum; in 37 of these 52 patients, the cholesterol concentration became normal. The hypercholesterolemia increased in 1 of the 53 patients (from 250 to 260 mg.). In 1 patient the cholesterol concentration increased from normal (210 mg.) to a hypercholesterolemic level (225 mg.).

It has been argued that the restriction of salt has no effect on hypertensive vascular disease. Therapeutic results such as those of Allen and Sherrill[10] and of Volhard[11] have been explained by Fishberg[12] on the assumption that salt-poor diets, because of their unpalatability lead to restriction of caloric intake and thus to reduction of the metabolic

TABLE III—CONCENTRATION (GM.) PER 1000 CC. OF URINE OF PATIENTS ON "NORMAL" DIET AND ON RICE DIET

| | *Normal Diet* | *Rice Diet (after 2 months)* |
|---|---|---|
| Urea N | 12 | 1.1 |
| Chloride | 6 | 0.1 |
| Sodium | 4 | 0.01 |
| Potassium | 2 | 3.0 |
| Sodium/Potassium Ratio | 2 | 0.003 |

rate. According to Page,[13] the effects obtained were due not to salt restriction, but to rest in bed, and the "psychotherapy of constant attention."

With the rigid restriction of sodium and chloride in the rice diet, the sodium and chloride excretion in the urine decreases to minimal amounts. In the urine of patients who have followed the rice diet for one month or longer, the average chloride concentration is about 100 mg., the sodium concentration about 10 mg., the potassium concentration about 3 Gms. per liter, i.e., the potassium concentration is slightly higher than that in the urine of patients on an ordinary diet, the chloride concentration is decreased to about 1/60, the sodium concentration to about 1/400. The sodium-potassium ratio, which in the urine of patients on an ordinary diet is about 2, decreases on the rice diet to 0.003 (Table III).

Grollman and Harrison repeated some experiments with the rice diet, using rats with experimental hypertension; they confirmed our finding, that the rice diet leads to marked blood pressure reduction.[14] Since the hypotensive effect was not obtained when the strict rice diet was changed by the addition of NaCl (not of KCl), this hypotensive effect was ascribed by the authors merely to sodium restriction. Unfortunately, no sodium, potassium, or chloride determinations in blood or urine were made.

No matter which single factor in the rice diet is of greatest importance in compensating the various manifestations of renal metabolic or excretory dysfunction, it remains true that in 203 of 322 patients,

TABLE IV

B 50182

White married man. Born 1902. "Always healthy until 1939." Blood pressure checked at two year intervals since 1927. B. P. known to be normal in 1936.

1939 Blood pressure elevated. Treated with Barbiturates.

March 1940 NEW YORK HOSPITAL B.P. 200-165/135-105.
Retrograde pyelograms: "Normal."
*"Hypertensive vascular disease."*

January 1941 PRESBYTERIAN HOSPITAL, NEUROLOGICAL INSTITUTE
*"Hypertensive cardiovascular disease."* B. P. 200/140.

February 1941 ROCKEFELLER HOSPITAL B. P. 200/140.
Variations: 196-174/140-120.
*"Hypertensive vascular disease; arterial hypertension."*
Daily injections of Tyrosinase intravenously for 23 days: Slight decrease in B. P.
Daily injections of Tyrosinase subcutaneously for 13 days: Decrease in B. P. to 150/100.
After one week, B. P. at previous level.
November 1941 B. P. 200/140.
During Tyrosinase treatment: B. P. 164/110.
Because of severe shock-like reaction, Tyrosinase therapy discontinued.

MASSACHUSETTS GENERAL HOSPITAL (Dr. Smithwick):
Lumbodorsal sympathectomy (Dec. 1941-Jan. 1942).

| | BLOOD PRESSURE DATA | | | EKG |
|---|---|---|---|---|
| | *Admission* | *Lying* | *Standing* | |
| Dec. 1941 Before sympathectomy | 172/135 | 180/134 | 186/145 | 12-18-41 $T_1$ upright |
| Mar. 1944, 26 mos. after sympathectomy | 204/144 | 196/140 | 150/123 | 12-29-43 $T_1$ upright |

Beginning 1945 Therapeutical trial with Testosterone: *"Blood pressure higher."*
March 31, 1945: DUKE HOSPITAL Admission 220/132.
(All B. P. readings taken while lying.)
March 31 - April 19, 1945: Average of 20 days in hospital on 1500 cal. reduction diet:
B. P. 197/129.
PSP (total excretion in 2 hours): 62%.
Urea clearance: 125%.
$T_1$ diphasic. Transverse diameter of heart 14.8 cm.

April 20, 1945: Rice diet started.
Averages:

| | | |
|---|---|---|
| May 15-21, 1945 | 129/94 | June 1, 1945 full time job resumed. |
| July 1945 | 125/90 | |
| August 1945 | 120/87 | |
| September 1945 | 126/88 | |
| October 1945 | 129/87 | |
| November 1945 | 128/89 | |
| January 8-14, 1946 | 128/91 | $T_1$ upright. Transverse diameter of heart 13.9 cm. |

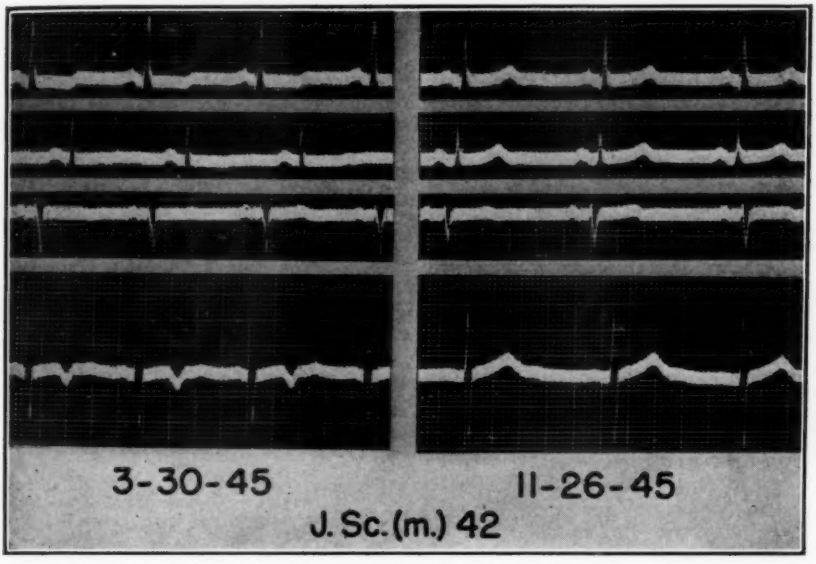


Fig. 1. J.S. (m. 42) "Hypertensive Vascular Disease." Rice diet since 4-20-45. No digitalis. Diphasic T 1 has become upright.

on most of whom other forms of therapy had previously been tried, the rice diet led to objective improvement.

Of 100 patients with primary kidney disease, 65 per cent showed improvement on the rice diet. Of 222 patients where a diagnosis of hypertensive vascular disease was made, 62 per cent improved.

Those who question the value of diet in the treatment of hypertensive vascular disease say that in those patients who responded to the diet our diagnosis was probably incorrect. I think that in most cases the differential diagnosis presents no difficulties. Table IV shows the summary of a typical history.

It would not be right to use such a case as an argument against sympathectomy. I have seen marked blood pressure reduction following sympathectomy, in patients with severe hypertension, and I have seen patients whose blood pressure was not improved. But I do think that the sequence of surgical treatment and dietary treatment should be reversed since the treatment with the rice diet, if it proves to be ineffective, can simply be discontinued.

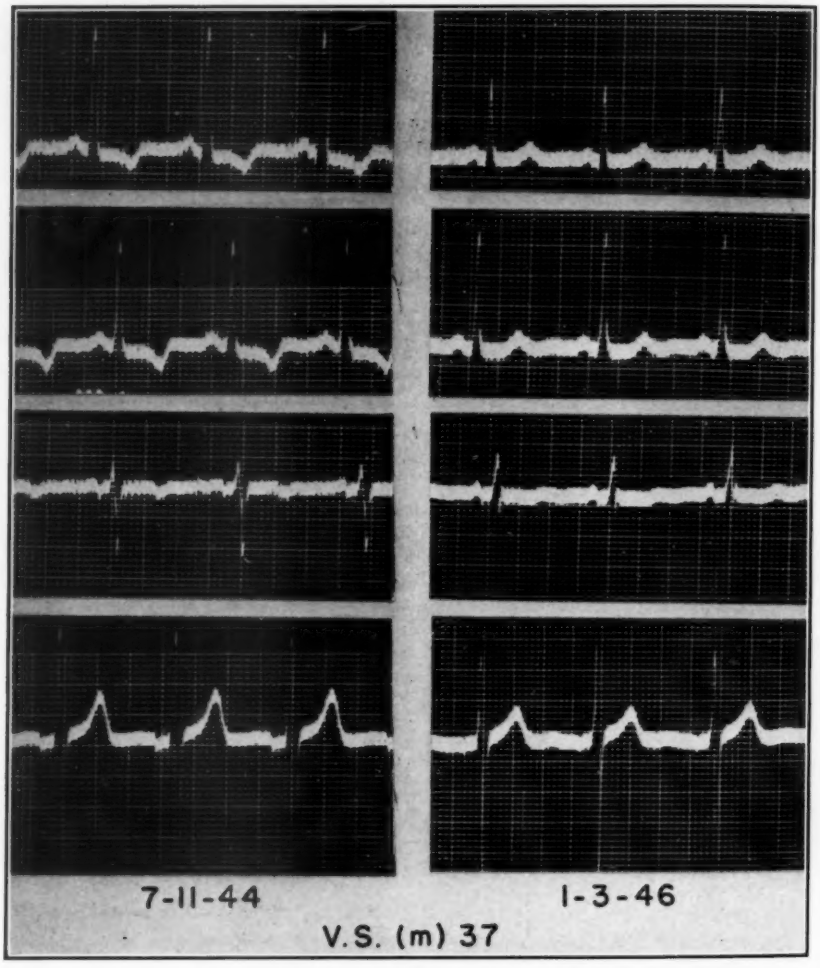


Fig. 2. V.S. (m. 37) "Hypertensive Vascular Disease." Advanced retinopathy. Rice diet since 8-16-44. No digitalis. Change in electrical axis. Inverted T 1 has become upright.

In the patient just mentioned, in spite of the sympathectomy, the electrocardiogram began to show myocardial involvement. T 1 which in December 1941 and December 1943 was upright, had become diphasic by April 1945. With the rice diet, however, the diphasic T 1 reverted to normal (Fig. 1).

We have studied the electrocardiographic changes in 100 patients

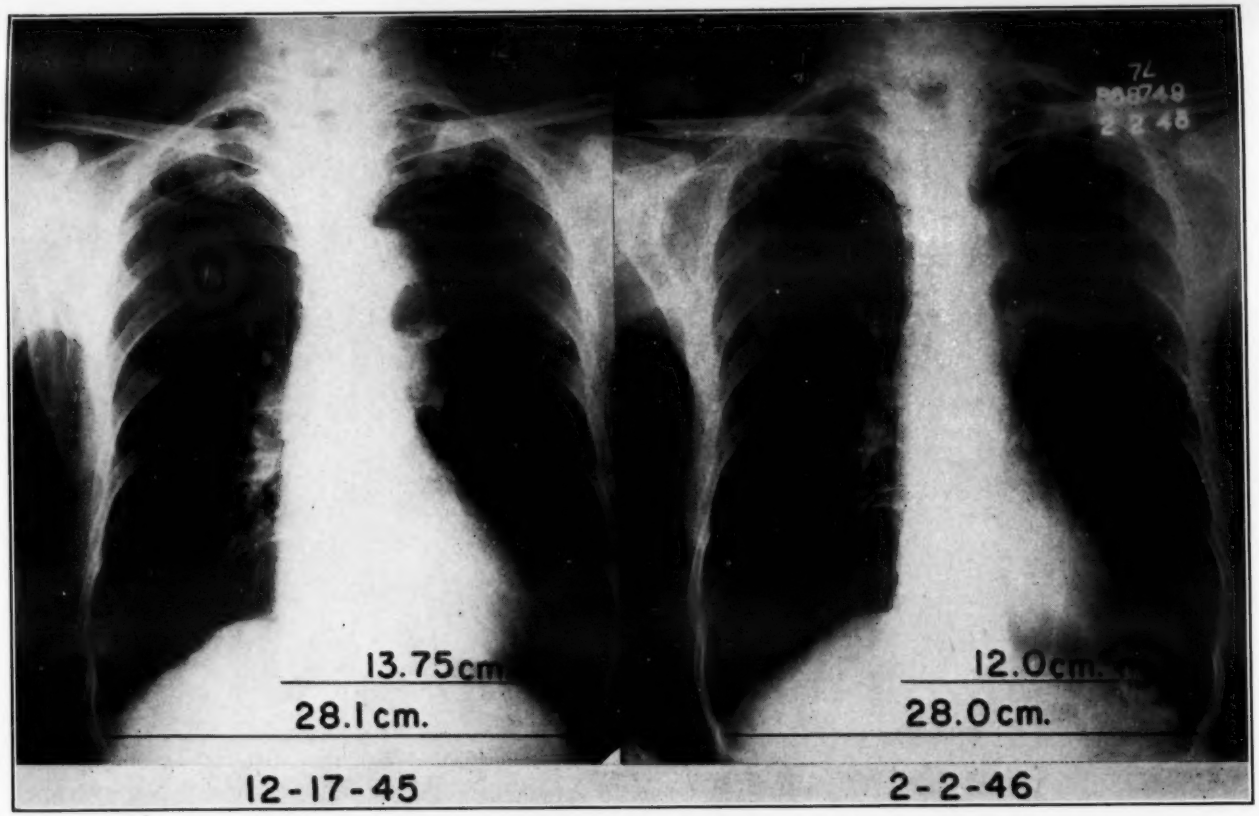


Fig. 3. McD. (m. 62) "Hypertensive Vascular Disease." Rice diet since 1-6-46. No digitalis. Reduction of heart size with change in transverse diameter of 14 per cent.

with hypertensive vascular disease, who have followed the rice diet for two months or longer. In 31 of these patients, the T 1 waves were completely inverted before treatment. In 11 of these 31 patients, T 1 became normally upright with the diet (Fig. 2). In no patient did the reverse occur. The shortest time in which a completely inverted T 1 became upright was two months, the average was six months.

In 77 of 87 patients with hypertensive vascular disease, the heart became smaller in size (Fig. 3). The average change in the transverse diameter was 10.1 per cent. The average chest diameter decreased by less than 0.7 per cent.

In 10 of the 87 patients the heart became larger. In these the transverse diameter of the heart showed an average increase of 2.5 per cent. The average chest diameter increased by 0.54 per cent.

I am sometimes told that enlarged hearts in hypertensive vascular disease become smaller "spontaneously," that electrocardiograms became normal "spontaneously," and that papilledema, hemorrhages, and exudates in the retina disappear "spontaneously."

I have not been fortunate enough to see many of these "spontaneous" recoveries, but I have often seen blindness as a result of advancing vascular retinopathy and death from heart failure, myocardial infarction, renal insufficiency, or cerebral vascular accident in patients who were not willing to submit to any drastic form of treatment because they believed that their disease would clear up spontaneously or that at least it would not become worse.

I have shown you some electrocardiograms and chest films of patients with hypertensive vascular disease who were treated with the rice diet. I will close this talk by showing you a few photographs of eyegrounds (Fig. 4). Forty-four patients with hypertensive vascular disease who had papilledema, hemorrhages or exudates, followed the rice diet for two months or longer. In all of them the retinopathy was arrested. In 20 of the 44 patients papilledema, hemorrhages, or exudates cleared up partially, in 20 completely.

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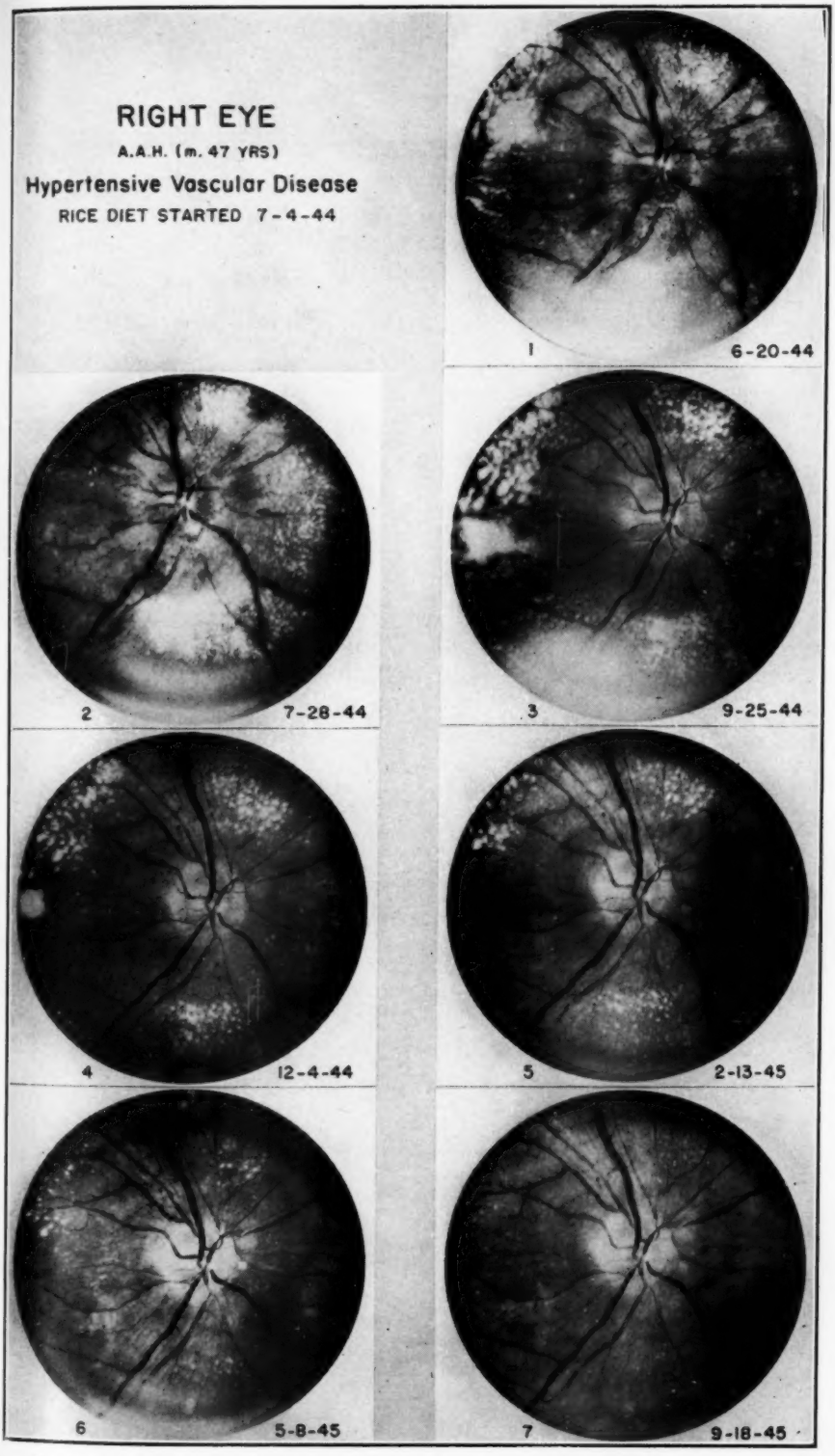


Fig. 4. A.A.H. (m. 47) "Hypertensive Vascular Disease." Rice diet since 7-4-44. *Right eye:* Disappearance of papilledema, hemorrhages, exudates.

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# PATHOLOGY, OLD AND NEW*

*Middleton Goldsmith Lecture, New York Pathological Society*

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## INTRODUCTION

No compliment that might be paid by the New York Pathological Society could quite equal that of the invitation to deliver the Middleton Goldsmith Lecture on this occasion. No words could fully express the deep sense of gratitude I feel for the honor of making this address, a task I face with all humility. The remarks of Gregg[1] at another celebration apply equally well here. "Without aspersions on lesser anniversaries we may well at once declare that no celebration can equal the first centenary. You are still young enough to glory in your age, yet old enough to boast of your powers of endurance. You are so encouraged by your stout survival as even to flirt with ideas of going on forever." The congratulations and best wishes of all those interested in pathology, not only for itself but for its meaning to medicine and biology, are due this Society.

## SOCIETIES FOR PATHOLOGY

It is said that Riva, physician to the pope, founded a society for pathologic anatomy in Rome in the middle of the seventeenth century and established a museum, but the record is not altogether convincing. In keeping with the notable accomplishments of France in pathology in the first part of the last century, the Société Anatomique of Paris was established under the guidance of Dupuytren in 1803. It survived only five years, the president for the final year being Laennec. It was reconstituted in 1826 with Cruveilhier as president and is the oldest society in the world with a dominant interest in pathology. Riesman[2] states that a pathological society was formed in Philadelphia in 1839,

* Given December 15, 1944 at The New York Academy of Medicine on the 100th Anniversary of the New York Pathological Society.

From the Institute of Pathology, Western Reserve University and University Hospitals of Cleveland.

with William Wood Gerhard as president, the purpose being the exhibition of pathologic specimens and the preservation of suitable material in a museum. It lasted only a few years and no trace can be found after 1843. It seems certain that the New York Pathological Society is the oldest in continuous existence on this continent. Being a Philadelphian, and imbued with what might be called the lococentric spirit said to characterize that region, I would have been pleased to find that it had the oldest society devoted to pathology. Such may be true in a sense, but the society was evidently a feeble infant that could not outlive childhood. Nevertheless, injured pride is somewhat mollified by Riesman when in reference to the permanent society born in 1857, he says that Samuel D. Gross, the first president, was "the first real pathologist of this country."

Horner published a text on pathology in 1827, but the book written by Gross which appeared 10 years later was the first significant treatise on the subject in this country. It must be admitted, however, that Gross was principally a distinguished clinician rather than a career man in pathology. The same can be said of all those prior to Lobstein and of many after him. Thus the societies established in the middle of the nineteenth century could not be called societies or associations of pathologists because in this country there were no pathologists in our sense of the word. Perhaps that is partly the reason for naming the society pathological. The purist groans at the adjective because of its implication of disease in the very organization. In addition, the founders had not the advantage of the style advocated by the publications of the American Medical Association; otherwise it might have been a pathologic society! It is of interest that the American Association of Pathologists and Bacteriologists was not formed until 1900, the American Society for Experimental Pathology until 1913 and the American Society of Clinical Pathologists until 1922. The Deutsche Pathologische Gesellschaft was started in 1898 and The Pathological Society of Great Britain and Ireland in 1906.

## What is Pathology?

In any discussion, it is wise to arrive at a general agreement as to terminology. In our times, it may well be said that a pathologist is a person who devotes his career to the study and practice of pathology. Dean[3] says the pathologist "should be able to say 'I am a pathologist;

I reckon nothing which appertains to disease is without interest to me.' To the pathologist all things, at any rate all medical things, are pathology." Be that as it may, we still should try to define pathology. I think we can agree that it is a subject pursued principally in the laboratory, utilizing all the tools of morphology, mathematics, physics, chemistry, physiology, bacteriology, immunology and the like to explain the origin, course and nature of abnormal form and function.

But what about the relation to the clinic and the living patient? Is the pathologist to be a savant in the sense of Richet,[4] one whose only object is the discovery of the truth? Evidently there are some who think so. Boycott,[5] for example, said at the dedication of the Pathological Institute at Montreal: "The time has now arrived when pathology must recognize that it is a science which can and ought to stand on its own feet and pursue its own end, which is the study of pathology, not the study of medicine and surgery." He went on to say that there are two sorts of pathologists, those whose real heart is in the clinical application and "those who are in pathology because they had it laid upon them to try to know about the reactions of living things to injury and disease" without any particular or direct reference to human welfare. Boycott lived in pathology as a science for itself and this attitude was shared in large measure by Oertel[6] and a few others. It can be said with assurance that most of us who give our lives to pathology do so because of the crowning place it occupies in the large field of medicine.

## The Theme

The central theme of this address is the evolution of the approach to pathology as it has advanced from the deductive reasoning of the earlier workers to the more profitable inductive reasoning made possible by the expansion of information in all fields of science. For the unfolding of this theme it seems profitable to undertake a cursory review of past achievements and to orientate us in relation to the time of the foundation of this Society. Subsequently, morbid anatomy will be discussed, to be followed by a glimpse into the future, prophetic or not as only time will tell.

## Historical Perspective

The history of pathology has been too well presented by Long,[7] by Krumbhaar[8] and others to justify a lengthy discourse here. That

would be presumptuous before this audience. I should, however, draw your attention to the fact that when this Society was born, there were few professional pathologists in the world; indeed none existed in this country. The very group which organized the Society, including Middleton Goldsmith himself, were essentially clinicians who realized the importance of pathology to medical practice and consequently gave the subject intimate study. Peters[9] called them pathologists but they did not devote themselves principally and primarily to the subject.

A history of pathology in ancient times, the middle ages, the renaissance and well into modern times is a story not of a special field but of medicine as a whole. Long[7] comments on the fact that during the 5000 years of the Egyptian dynasties, there must have been at least 750,000,000 bodies prepared for burial but the descriptions are devoid of references to morbid anatomy. Yet there is little doubt that the Alexandrians performed autopsies of a sort as indicated by the description of the woodeny or stony-hard liver with ascites, credited to Erasistratus. It is a sad circumstance that the records of the Alexandrian school are only preserved second-hand in the writings of Celsus. According to Singer,[10] the first frank reference to a postmortem examination was made "when, during the plague of 1286, one of the bodies was opened in order to determine the nature of the disease." In my survey of the subject I found little record of autopsies until the fourteenth century, when they were performed at Salerno, Bologna and Padua.[11]

In the sixteenth century, progress began with the dissections and autopsies of Vesalius, Eustachius, Paré, Donatus and Schenck von Grafenburg. During this time Antonio Benevieni recorded 20 postmortems, subsequently published by his brother. More important but less widely known is the book of Jean Fernel of Amiens whose volume VII entitled Pathologiae was the first codification that could be called a text on pathology (Long[7]). Not to be forgotten is the influence exercised by the development of printing, which in all fields permitted men to exchange, pool and transmit knowledge. Without this, inductive reasoning could not have evolved. Probably of equal importance was the beginning of political liberty in the founding of the Dutch Republic, for this carried with it the initiation of freedom of thought and of scientific research.

The seventeenth century provided such men as Bartholin, Malpighi, Glisson, Sylvius and that Riva who is said to have established a society

for pathology. In the latter part of that period Bonet or Bonetus published his "Sepulchretum," a landmark to be sure, excellent for its time, but now only of historic value.

The eighteenth century had many notable figures but for our purposes Morgagni, whose profile graces the seal of your Society, was the greatest.[12] His "De Sedibus," based on letters to a friend and then revised, appeared in 1761, when he was 71 years old. The autopsies were not systematic in our sense, but the publication showed a keen appreciation of clinico-pathologic correlation. John Hunter's protocols are more satisfactory, but still inadequate. The latter part of this century is marked by the publication of Matthew Baillie's atlas and text, to my mind the first to introduce real pathology in concrete form.

It was not until Rokitansky began his work that well systematized methods and protocols became prevalent. When he was 58 years old he performed his thirty thousandth autopsy and Long states that by the time of his death at 68, he had available the records of 70,000 autopsies. Some of you may remember Theodor, the diener at the Allgemeines Krankenhaus, who in my day said that in 10 years he had assisted at 30,000 autopsies. Perhaps George Taggart in his many years of faithful service at Blockley has had as great an experience. The vast material in Vienna was by no means the sole cause of Rokitansky's great contribution. He was a pathologist in the truest sense, even though his deductive interpretations were faulty. He brought pathology into the soul of melicine. His stimulus was so great that as Roessle[13] remarks, a small shabby dead-house in the furthest corner of the Allgemeines, "a wretched barrack" as Kussmaul called it, became the medical center of Vienna.

Our song of great men reaches a grand crescendo with mention of Virchow. Inspired by Johannes Müller, he entered pathology under Froriep and in addition to becoming a prosector of great skill began his investigations. We need not detail his work but can agree with Welch that the establishment of cellular pathology "marked the greatest advance which scientific medicine has made since the beginning."

## Chairs of Pathology

In the nineteenth century, when Bichat, Rokitansky and Virchow flourished, the first part was marked by the contributions of the French, including such men as Pinel, Corvisart, Laennec, Louis and others. A

most significant item, however, was the creation of the first chair of pathology in 1819 at Strasbourg, during one of the times when it was French. This was created at the suggestion of Cuvier and occupied by Lobstein, the first chair devoted solely to pathology. Seventeen years elapsed before Dupuytren suggested the chair at Paris, which Cruveilhier occupied in 1836, and another decade passed before the establishment of the chair at Würzburg, created for Virchow when his revolutionary ideas forced him to leave Berlin. In the meantime, Carswell occupied the chair of morbid anatomy in London in 1831 and Johannes Wagner became extraordinary professor at Vienna in 1832. Berlin awaited the return of Virchow in 1856. Chairs were established at Harvard in 1847, Pennsylvania in 1867 and at the College of Physicians and Surgeons in 1875. It was later, however, that the professors devoted their full time to the subject. But as Krumbhaar[8] says, before the close of the century "every self-respecting medical school had an independent chair for this important subject."

## Orientation of Founders

If time permitted, the general cultural level of our country in the 1840's might be reviewed, but we should recall the limitation of communications, no telegraph, no telephone, dreadful roads, railroads not to be important for 20 years, ill-paved streets, poor water supplies, inadequate sewerage, not even gaslight or bath tubs. No radio, no jukeboxes, no ice cream cones, none of the accretions of our modern civilization! And yet these things were not missed by our rugged forebears.

Where did pathology stand in 1844? Bichat, Corvisart, Pinel and Laennec were dead. To be sure, Brettoneau, Louis, Broussais, Charcot, Claude Bernard and Brown-Séquard were living, but the genius of pathology was surely moving to Britain. The Hunters and Matthew Baillie had died but Carswell, Hodgson, Bright, Addison, James Paget and Hodgkin were active as was also Gull in Ireland. Only seven years had elapsed since Gerhard had distinguished typhoid from typhus largely on the basis of pathologic anatomy. Soon the mantle of our "Fach," migrating from Italy to France to England would fall on Germany.

Already Johannes Müller had as pupils Schwann, Henle and Virchow. The cell theory resulted in the publication of books on patho-

logic histology, by Vogel in 1843 and by Lebert in 1845. Johannes Wagner had died but his pupil Rokitansky was bringing out the great Handbuch during the forties. Virchow had been graduated in medicine just a year, but the Archiv known by his name began publication in 1847. Yet to develop were his pupils Cohnheim, Klebs, von Recklinghausen, Rindfleisch, Ponfick, Orth, Hoppe-Seyler, Salkowski and others. Weigert was born in 1845 and Ziegler in 1849, Schmorl in 1861, and Aschoff in 1866. In our country, Delafield, Prudden, Welch, Councilman, Mallory, Ewing, Hektoen, Flexner, Wells, Pearce and many others with names made familiar by their work had yet to appear on the horizon. Theobald Smith was not born until 1859 and his reports on cattle fever of Texas did not appear until 1890, the first convincing proof that arthropods can be vectors of disease. Pathologist, bacteriologist, parasitologist, immunologist, scholar, savant and practical scientist, kindly gentleman, he was to my mind the greatest figure American Medicine has yet produced. William Bulloch[14] said: "It is certain that America in days to come will look at him with that veneration with which France cherishes the name of Pasteur and Germany that of Robert Koch."

## Deductive and Inductive Reasoning

A little later than the time of the founding of this society occurs the dividing line in pathology between deductive and inductive reasoning, the line between pathology, old and new. The investigators of the remote and even recent past were obliged to employ deductive thinking, or the analytic form of reasoning. Thus a group of symptoms and signs was correlated with anatomic observations. Our forebears had not a sufficient number of instances to set up generalities from which subsequently to synthesize their information. Nor did they have chemical, physiologic or other facts on which they could base inductive reasoning. Even up to recent times, the correlation of the clinical manifestations and morphologic demonstrations was based on deduction and seemed sufficient; those who studied medicine in the early part of the current century will recall that much of their instruction was thus founded. A concrete illustration of the defects of the method may be given by reference to the studies of Richard Bright, who observed the association of the hypertrophic heart with chronic renal disease. The one accompanied the other, but why that was true could not be ex-

plained with the information available in his day. Purely as theory he suggested the importance of peripheral resistance. The intervening phenomena were unknown to him because physiology had not explained the stimulus to hypertrophy offered by stretching of hollow muscular organs; diastolic stretching of the chambers of the heart was not in the picture. A century had elapsed since Stephen Hales had shown that there is pressure within the arteries, but another century was to elapse before readings of blood pressure were common clinical practice. Bright thought of a chemical stimulus to the heart, but even now the exact basis of hypertension is not fully clarified.

The pathologist and, as Prudden[15] put it in a letter to Ewing, "his satellite, the practitioner" must necessarily await the development of instruments of precision, of chemistry, physiology, and ancillary sciences in the biologic field, before inductive reasoning could be practiced. W. W. Keen[16] has emphasized the significance of instruments of precision in the advancement of science and human welfare. To us as pathologists, the microscope takes first place in this category. Haden[17] says: "the name microscope was given by a physician; a physician was the first to make practical use of the microscope; three of the five great microscopists of the classical period were physicians." Nevertheless, this instrument was most widely used by laymen. More than a decade after this Society was founded, Carpenter[18] said in the preface of his book that the microscope served both for scientific research "and as a means of gratifying a laudable curiosity and of obtaining a healthful recreation." Roger Bacon used a simple lens and Leeuwenhoek improved it by shortening the focal length. There is general agreement that the first compound microscope was made by an optical worker, Zacharias Janssen, about 1590, at Middeburg on that island of Walcheren so recently subjected to the fury of war. This instrument enlarged objects nine diameters. Robert Hooke built a better compound microscope in 1665, but it was not until 1693 that magnifications of 100 diameters were produced by Marshall and not until 1716 that Hertel used a reflecting mirror. Schlumberger[19] states that in 1807 van Deyl "produced a satisfactory compound microscope with an achromatic objective and a magnification of 229" diameters. But the history of the microscope as we know it is more recent.

Policard[20] starts the story in about 1848 in the town of Jena, four years after your establishment in 1844. The achromatic lens had already

been produced, but the microscope was not yet sufficiently precise. Karl Zeiss was a builder of scientific apparatus, employed in the laboratory of physics at the University of Jena. He enlisted the aid of Ernst Abbe, Professor of Medicine in the University, who with help of the mathematician Magnus, planned the sub-stage condenser. Zeiss and Abbe ultimately realized the necessity for good optical glass which was finally produced by Schott. This group working through the years ultimately created the modern compound microscope, with its illumination, optical precision and resolution, about 1872. The development of the stereoscopic microscope, the binocular microscope, the ultra-microscope, the petrographic microscope and its modifications, the telemicroscope and the electron microscope naturally followed.

Provisions for sectioning and staining are even more recent. The freezing of tissues for sectioning was first practiced about the time this society was founded, but the sections were made free-hand or by the Valentin double-bladed knife. Objects were embedded in paraffin by Klebs in 1869 and in celloidin by Duval in 1879. The mechanically precise microtome was probably first used by Thoma in 1881. Although Hannover used chromic acid for fixation in 1844, yet Flemming's fluid was not announced until 1882, Zenker's fluid in 1894 and formalin in 1893. Staining by alum carmine was done by Gerlach in 1858, but alum hematoxylin was not used until 1865. Eosin was first used as a counterstain in 1875. Von Recklinghausen used silver salts, but for modern staining methods we are indebted particularly to Weigert and to Ehrlich, and in this country to Mallory. Smith[21] gives an excellent bibliography. The society was at least half a century old before pathologists had at hand microscopic sections thin and well stained and a satisfactory microscope with which to study them.

The use of experimental methods in the study of problems in pathology was carried on by many early investigators, notably John Hunter, but the beginning for professional pathologists was the work on migration of leukocytes reported by von Recklinghausen in 1863, to be followed by his experiments on inflammation in the cornea of the frog in 1867. More impressive and the keystone of this type of work was Cohnheim's publication on inflammation and suppuration in 1867, also in part on the frog cornea but particularly on the frog mesentery. Here for the first time were explained the phenomena of exudative inflammation. Cohnheim showed the influence of the vascular system,

"ohne Gefässe, keine Entzündung" and identified the leukocyte as the forerunner of the pus cell. This was followed by the work on thrombosis, embolism, infarction and other topics. Welch brought the inspiration of his teacher to America, where the experimental method by the end of the nineteenth century had taken root and flourished. MacCallum[22] wrote about his course in 1906, 1907 and 1908. This was followed by Pearce's report in 1911[23] and then by numerous others, including a handbook on the subject by Wagoner and Custer.[24] Richard Pearce said that: "The great continuous advances in medicine . . . resulted from organized laboratory effort based on the principle of exact experimental methods."

These applications of the experimental method were made increasingly useful with the strides in the latter half of the nineteenth century and subsequently, of pure science, chemistry, physiology, bacteriology, immunology, etc., including recently the study of hormones and nutrition. In the latter connection witness the investigations on tumors of endocrines and the explanation of the origin of Laennec's cirrhosis.

These various techniques, facilities and basic information were not available to the founders of this society, to their predecessors or their immediate successors. They were limited to deductive reasoning. Paraphrasing Pack and Brooks,[25] the morbid anatomist of the old days depended on deductive reasoning based on his extensive experience in morphology, but his successor reasons inductively because of his better basic foundation.

Note that I have avoided the terms experimental pathology, pathologic physiology, pathologic chemistry and the like. This is deliberate because I believe that these implements are readily available to the pathologist. Many of the techniques can be mastered by the educated pathologist, and in his hands become the tools of study and research. In modern institutions, collaborative research is possible when the pathologist does not or cannot acquire skill in the more complex procedures. He often needs guidance in methods and aid in interpretations, but always his studies are directed toward the understanding of disease.

No study of disease can be informative and satisfactory without incorporation of etiology. Causative factors may be predisposing and precipitating, but as Gregg[1] indicates a third factor is also important, namely perpetuating. The last is of especial importance in reference to chronic disease of any kind, mental or organic. It must be significant in geriatrics, a field assuming magnitude in our aging population.

The development of chemistry, physiology and experimental methods has gone along with bacteriology and immunology. Thus etiology has progressed. Pathologists can now interpose developmental mechanisms between cause and effect. This is the province of inductive reasoning, based on a premise of collected facts. Pathologists can also think in terms of causality, a broader conception than cause. For every cause there is a causal connection before the effect. Oertel,[26] whose philosophic comments have often failed of the recognition they deserve, says that: "Roux, the founder of evolutionary mechanics, insists that every causal knowledge of a phenomenon must include a complete connected chain of events which are responsible for it." I refer to Oertel further because of the validity of his views. The series of events leading to an effect must be put in their lawful order. Every occurrence bound to a sum of circumstances necessitates the occurrence. To say that a certain bacterium causes a certain disease gives no information about the manner, sequence and mechanisms of the events, and is not satisfactory to the critical mind. He quotes Tendeloo's definition of pathology as the science "of disease producing constellations." The doctrine of causality must be utilized if etiology is to fill its place in pathology and medicine. It can furnish links in the chain of predisposing and exciting factors and particularly in reference to those perpetuating factors now in the foreground. Causality must occupy a large place in inductive reasoning.

In passing I cannot refrain from mentioning Oertel's strictures on teleology, the exact opposite of inductive reasoning and causality. The term comes from the Greek telos, meaning goal or purpose. "It is commonly stated that a thing happens in the human body because it serves a certain (generally beneficial!) purpose; that is, the end result is taken as an explanation of the mechanism of its occurrence. . . . A thing happens in nature, . . . because a causal chain of preceding events necessitates it." Teleology adds nothing to precision of thought or exact inquiry, I have said: "The doctrine of purpose should not be permitted to smooth too easily the paths of learning, especially if this entail a sacrifice of the critical analysis of cause and effect." Even the teleologists are put to it to find anything beneficial in the growth of malignant tumors! Scientific progress and teleology are permanently at odds.

## Place of Morbid Anatomy

Does this discourse on deductive and inductive reasoning, the application of functional studies and the logic of causality mean the abandonment of morbid anatomy? Rous[27] reached the climax of assent in one of his early papers when he referred to morbid anatomy as "the dried stockfish of the subject," and his condemnation echoes that of several others. But let us look elsewhere. Boycott,[5] that advocate of pathology for its own sake, says that pathology began with morbid anatomy "and in this still finds its fundamental basis." Further, "the quaint notion that morbid anatomy is played out comes only from those who are ignorant of what the anatomist has to say." Turnbull[28] in his obituary notice of Schmorl comments that "to those who had been taught in England that morbid anatomy was a dead subject the first few days with Schmorl became an unforgettable revelation." Roessle[29] says that "Pathologic anatomy remains the supporting pillar of the giant growth of medicine." F. von Müller,[30] who did more to establish the modern clinic than any other single person with the possible exception of Osler, in his retrospect in 1937, expressed the view that Corvisart in France and Rokitansky in Austria put pathologic anatomy in the foreground of medical thought, and thus furnished the basis for modern medicine.

Morphology does not disclose the disease as such, but as MacCallum[31] said, it furnishes "the changes underlying the manifestations of disease." We may go further and say that for most conditions, morphology serves better than any other method for the identification of disease. This is illustrated in the daily life of the pathologist with his autopsies and surgical specimens. All thoughtful clinicians depend in large measure on this well established fact and it is often basic to clinical research. Morphology is fundamental to research in pathology. The time has not passed, in my opinion, when it cannot add its own contributions to advance in pathology as well as the broad field of medicine. Furthermore much of research in pathology by the experimental method depends on morphologic identification of lesions produced. The newer knowledge of hepatic cirrhosis, of hypertension, of avitaminoses and other conditions depends on morphologic identification. Nowhere is this less true than in experimental investigation of neoplasms. Rous himself, in spite of his earlier scorn of pathologic anatomy, has published beautiful illustrations of the tumors he has so well studied. I am

convinced that morbid anatomy is of the utmost importance to our subject, that the tutelage of our pupils must be largely devoted to training in this field, that in itself it is a place for exercise of skill and judgment, and that no one can be called a pathologist unless he is trained, experienced and competent as a morphologist. He cannot adequately perform hospital duties, teach, or engage in research without pathologic anatomy. It is not dead, it is living, progressing and holds much for the future.

That morphology is all of pathology cannot be maintained and I agree with Symmers[33] who says: "That individual who confines himself to the study of pathologic anatomy without attempting to bring it into harmony with the signs of altered function is blind in one eye." Even we cloistered laboratory workers realize that monocular vision is devoid of perspective, and without perspective the pathologist cannot fill his place in the cosmos. The rapid advance of pathology in recent times has been due as Klotz[12] says, to "utilizing the principles of chemistry, physics and biology, but wedding none of these to the exclusion of the other." I still insist that pathologic anatomy has furnished the ground work for most of the advances in medicine and pathology, continues to do so, and when properly pursued will do so in the future both for its own sake and as a foundation for functional studies.

## Future of Pathology

And finally, what of the future? That, in my opinion, depends upon pathologists rather than pathology. The subject has become so vast that no one person can master its entire scope. Yet all can have a broad interest in the whole field and can do his share, great or small, in its progress. It is a truism to say that if it remains static, it does not only fail to advance but retrogresses. Those satisfied with the present are a hindrance to all the others.

Kracke[32] sets up five groups of pathologists. (1) Teachers, who may be confined in academic seclusion. (2) Hospital pathologists covering all divisions of laboratory medicine. (3) Hospital pathologists for a group of smaller hospitals. (4) Pathologists in private practice with few autopsies. (5) Governmental pathologists. He overlooks the pathologist engaged in a privately supported institute for research. I think the divisions may be simplified. There is the pathologist who because of his academic, governmental or research post has the interest,

material associations and facilities to be a productive investigator. He is comparable to the full time clinician. He must be expert in the broad field even though his research may be highly specialized, but he leads in and guides acquisition of knowlelge. In contrast is the pathologist in hospital or private practice, who can be compared with the clinical practitioner; and these are on the "firing line" of medicine.

In the first group may be included the professor of pathology in the medical school and the institutional research worker. The former is in a position of serious responsibility. He represents pathology in an educational institution and its associated hospitals. To do so he must be a master of his subject, a referee in pathologic diagnosis, an inspiration to a rising generation of physicians, a scholar and investigator. The position of pathology in the curriculum, joining together the laboratory sciences and the clinics, forces him to be in the forefront of medical education; he should be an educator. This qualification has led to his appointment as dean in many instances. Parenthetically it may be said that if this duty benefits pathology, except through its supposed prestige, the advantage is not fully apparent. The professor exercises his influence not merely through medical students but also in significant degree through those graduates who are associated for a short time in preparation for a clinical career or for a longer service in training for a life work in pathology. That these ideals can be fulfilled in great measure, even in our land, is illustrated by such figures as Welch, Prudden, T. Smith, Ophüls, Councilman, Mallory, Pearce and Wells, to mention only some of those no longer living.

The pathologist in the research institute, governmental or private, is charged with much the same responsibility, save for instruction of medical students, and should possess much the same qualifications. He must be armed "with the intellectual habits and the methods of 'pure science' that he may be fit to cope later with the impurities of nature" (Rous[27]). In addition he must be blessed with initiative and fruitful imagination, for upon him much of the progress of pathology depends. He should leaven the whole institution, not only by his own work and his aid to other investigators, but also by that critical turn of mind which characterizes pathologists more than any other group. His addresses and publications enlighten the profession and ultimately the public. His release from routine gives him extraordinary privileges in the way of research, a greater freedom than is possessed by other pathol-

ogists. His opportunities put him out in front and entail large responsibilities not only in his selected field but in pathology as a whole.

The practicing pathologist in the hospital usually carries a heavy load of routine. He too should be a master of his subject in order to lend his aid in diagnosis and treatment. That he can possess equal facility in all divisions of pathology is not to be expected, but at least his training and experience should make him dependable in what has been called "tissue diagnosis" and competent to direct all the other activities. He represents pathology in his institution and his community. His laboratory should be "the axis about which the scientific work of the hospital revolves" (Simpson[34]). The private practitioner of pathology should be similarly motivated.

The future of pathology depends in large measure upon the skill, thoughtfulness and precision with which this routine worker integrates his activities with the general medical procedures of his institution and professional community. In the welter of the daily job he must maintain and impart the scientific habit of thought.

The future of pathology depends also on the academic pathologist. The impression he creates on students, colleagues and the community, will influence the respect in which his field is held. The same is true of the pathologist in the research institute. That impression, to be favorable, must be based upon the solid substance of the pathologist. He must be well informed, well trained, energetic, of broad vision and sympathetic. Form of expression is also important, but no superficial accomplishments can replace basic realities.

The future of pathology depends also on research. There are those endowed with that insatiable curiosity which for its satisfaction demands investigative study. Curiosity is "probably the outstanding characteristic of modern thinking" (A. Flexner[35]). The drive for production is a corollary of curiosity, and it brooks interference only with impatience. Nevertheless, circumstances often determine how far and well this inherent urge can be satisfied. Obviously, opportunity is greatest in the research institute and often excellent in the university, but all too frequently least in the general run of hospitals. Then too the personnel differs, because appointment to these various types of position is often by natural selection. But of this I am sure, that if the urge exists, research will be accomplished, even though limited by burdens of routine, lack of facilities and some limitation of mental endowment. The hospital

pathologist may not carry on intensive continuous investigative studies but he invariably can, if he so desires, make contributions of greater or lesser importance to the sum of human knowledge. Being a fine pathologist aids in his selection of projects but at the same time adds to his responsibility to further the general lore of his subject, through dissemination of information which he collects. A good case report is not to be scorned; in itself it may have importance and when added to others may furnish a collected series of great value. We must admit, however, that a good routine job may be done without high scientific attainments.

From the viewpoint of significance, the publications of the institute or academic pathologist usually have great weight, but from the viewpoint of human welfare, the hospital pathologist can be eminently useful. To be sure there is an aristocracy of the intellect and correspondingly an aristocracy of pathologists. This is not determined by participation in societies and meetings but by attainment in scientific pursuits. It should not justify envy or awe on the part of the less fortunate nor an attitude of superiority on that of the distinguished investigator. Mutual respect founded on a clear conception of the aims of all groups, will go far in preserving and advancing pathology.

"I do not choose" to discuss economic questions. It would be stupid to ignore this matter entirely. Funds must be made available if pathology is to advance. Salaries must be sufficient for the pathologist and his family; the best work can be accomplished if personnel is reasonably free of financial worry. Money alone can provide space, equipment, materials and all the intricate facilities necessary. Young people may enter the field without foreknowledge of their future, but they do not stay unless they have reasonable assurance that if they survive competition they can face their careers with a certain degree of equanimity. Nevertheless, in my opinion, the economic aspects are largely dependent on the pathologist himself and what he can offer to science and medicine.

We have pointed out the migration of the major activity in pathology from Italy to France to England and to Germany. On what shoulders will the mantle next fall? Where will the muse bestow her blessing, her genius, her opportunities and her responsibilities? Will it move east to Russia or west to America? Prophecy is futile, but we have the example of a coincidence of decline of German pathology, in spite of Aschoff, Roessle and like spirits, and the rise of National Socialism. No

one can say with certainty whether this concurrence is due to politically instigated materialism and insistence on immediate application of science or whether it is in large part economic. In either event it is attached to loss of freedom of the investigator and teacher. Germany in the last decade and a half has lost sight of that truth so well enunciated by Abraham Flexner in his address, "The Usefulness of Useless Knowledge."[35] Applied science, whether in medicine or other fields must have its backlog of pure science, truth for its own sake. Only freedom of research can furnish this fund of basic information and only freedom can guarantee its wisest and most fruitful application. If Russia were to grant such freedom, she might well inherit the mantle, or at least part of it. We must see to it that the muse which has shown us her favor in in the last half century does not pass us by. She will only grant us her further benefactions provided her devotees are not shackled.

## Epilogue

Your kindness and patience have allowed me to review the background of pathology, to orientate the time of the establishment of the New York Pathological Society in the history of our field and to point out that the evolution of science in general has permitted the change from deductive to inductive reasoning, the milestone that divides the old pathology from the new.

I hope you share my conviction that pathology has great promise, but that fulfillment and performance depend on the pathologists themselves, their quality more than their numbers, their inherent merits, their ability and their rigid integrity. With Link,[36] we can wisely advise "the struggle for improvement rather than the guarantee of perfection, the adventure of achievement rather than the certainty of success." It is for us and our successors to guard the tower and keep the faith, a task in which this distinguished Society, according to its history and tradition, will share in full measure.

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